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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,384	06/08/2006	Ruediger Ridder	05033.0010.PCUS00	7072

27194 7590 08/01/2008

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ART UNIT	**PAPER NUMBER**
1643	

MAIL DATE	DELIVERY MODE
08/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,384	RIDDER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-47* is/are pending in the application.

4a) Of the above claim(s) *46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060428;20060608*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTO-90*.

DETAILED ACTION

1. The election filed April 1, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group V, claims 35-38, drawn to kits comprising reagents to detect a polypeptide.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In addition Applicant has elected with traverse the species of the invention of Group V, wherein the cell proliferation marker is Ki67 and the kit comprises a $p16^{INK4a}$ sample for carrying out a positive control reaction.

2. Claims 35-47 are pending in the application. Claims 46 and 47 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 1, 2008.

3. Claims 35-45 are currently under prosecution.

Election/Restrictions

4. The Ki67 antigen and the Ki-S5 antigen are the same antigen; accordingly to the extent that the claims are directed to a kit comprising probes for detecting this antigen identified as either Ki67 or Ki-S5, the requirement to elect one or the other has been withdrawn.

5. Applicant's arguments traversing the propriety of the requirement to elect a single species of the invention of Group V is acknowledged.

Applicant has argued that Ki67, Ki-S5, and Ki-32 are molecules necessary for the maintenance of cell proliferation and should be considered together.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

As mentioned above, the Ki67 and Ki-S5 antigens are one and the same.

Otherwise, each species of the invention of Group V is a patentably distinct kit comprising one or more probes for detection of at least one cell proliferation polypeptide marker in biological samples, wherein each one or more probes is a distinct set of reagents that function as probes of structurally and/or functionally disparate molecules. Accordingly, consideration of the merit of the claims, insofar as the claims are directed to any one species of the invention, requires a search that is different from that necessary to consider the merit of the claims insofar as the claims are directed to any other species of the invention. Moreover, the search that would be required to examine claims directed to any one species of the invention is not the same, nor is it coextensive with the search required to examine claims directed to any other species. As such, consideration of claims directed to more than one species would require more than one search; and any need to perform more than one search would constitute a serious burden. Therefore, the requirement is proper.

In further response to Applicant's argument that Ki67, Ki-S5, and Ki-32 are molecules necessary for the maintenance of cell proliferation, the biological role of Ki67/Ki-S5, in particular, has not been determined[1]; so it is not understood why Applicant has made such an argument. Nonetheless, each of the markers is detected with different probes; and furthermore, it appears that there are differences in the expression and localization patterns of the genes and their products in cells, which suggest that each has a different function.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statements

6. The information disclosures filed April 28, 2005, and June 8, 2006, have been considered. An initialed copy of each is enclosed.

Specification

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is ThinPrep™; see, e.g., page 26, line 5, of the substitute specification.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

8. Claims 37, 38, and 40 are objected to as being drawn in the alternative to the subject matter of non-elected species of invention.

9. Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 41, which depends from claim 40, recites, "wherein the cell proliferation polypeptide is Ki67. However, according to claim 40, the cell proliferation polypeptide is Ki67, Ki-S2, or Ki-S5. As such, the cell proliferation polypeptide of claim 40 may be Ki-S2, for example, and Ki-S2 is not Ki67, as

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[1] See, e.g., Bullwinkel et al. (*J. Cell Physiol.* 2006 Mar; 206 (3): 624-635); entire document (e.g.,

would be necessitated by claim 41. Consequently, claim 41 does not properly further limit the subject matter of the preceding claim.

It is suggested that this issue be remedied by amending claim 41 to depend from claim 35, as opposed to claim 40.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 42-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42-45 are indefinite for the following reasons:

Claim 42 and 43 are indefinite because claim 42 recites the limitation, “said labels", where there is no antecedent basis in the preceding claim (i.e., claim 35) to support the recitation. Since it cannot be determined to which labels the claim refers the metes and bounds of the subject matter that is regarded as the invention cannot be determined.

Claims 44 and 45 are indefinite because claim 44 recites the limitation, “said one or more probes (a)” and claim 45 recites the limitation, “said one or more probes (b)”, where there is no antecedent basis in the preceding claim (i.e., claim 35) to support the recitations. Since it cannot be determined to which labels the claim refers the metes and bounds of the subject matter that is regarded as the invention cannot be determined.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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the abstract; page 624, columns 1 and 2).

13. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis*

support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a genus of “probes”, which are suitable for use in detecting at least one “INK4a polypeptide” and at least one “cell proliferation polypeptide marker”.

Inasmuch as the claims are directed to the elected species of invention, the "probes" of which the kit is comprised must be suitable for detecting $p16^{INK4a}$ and/or Ki-67.

The specification describes the genus of “probes” as inclusive of antibodies that specifically binds to $p16^{INK4a}$ or Ki-67, but the genus includes any molecule (i.e., reagent) that might be used in the process of detecting $p16^{INK4a}$ and Ki-67.

The “probe” might be any molecule (e.g., a peptide, a small organic molecule, or any a ligand of any other material or structure), which binds to $p16^{INK4a}$ or Ki-67; or again it might be any molecule (e.g., reagent) that might be used to detect $p16^{INK4a}$ and/or Ki-67. The “probe” need not specifically bind to $p16^{INK4a}$ or Ki-67; it need not have any particular structure; and it need not have any particular function in an assay designed to detect $p16^{INK4a}$ and/or Ki-67.

The description of an antibody that specifically binds to $p16^{INK4a}$ or Ki-67 is not reasonably deemed representative of the genus of "probes", as a whole, considering the extent to which the structures and/or functions of the "probes" may vary.

Moreover, merely having described the genus of "probes" as a material suitable for the detection of $p16^{INK4a}$ or Ki-67 does not suffice to adequately describe the claimed subject matter with the clarity and particularity necessary to satisfy the written description requirement, or to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the invention was filed.

Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of "probes" that can be used to detect $p16^{INK4a}$, or any other "INK4a polypeptide", and/or Ki-67 or any other "cell proliferation polypeptide marker". A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in manufacturing the claimed invention does not fulfill the written description requirement. Then, too, recognizing that the claims are drawn to materials or substances that are suitable for use in detecting $p16^{INK4a}$ and/or Ki-67, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, e.g., the ability to detect $p16^{INK4a}$ or Ki-67, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the

genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a material or substance that can be used to detect $p16^{INK4a}$ and/or Ki-67; without such a material or substance, it is impossible to practice (i.e., make and/or use) the invention.

In addition, although the skilled artisan could potentially identify agents that might be used in manufacturing the claimed invention by screening for materials or substances that are capable of detecting $p16^{INK4a}$ and/or Ki-67, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991);

University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of materials or substances that are capable of detecting $p16^{INK4a}$ and/or Ki-67, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. Again, an antibody that binds to $p16^{INK4a}$ and/or Ki-67, which might be used in detecting $p16^{INK4a}$ and/or Ki-67, is not representative of the genus of "probes", as a whole; and furthermore, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Turning to a different issue, though the claimed "probe" need not be *an antibody* that binds to the "INK4a polypeptide" and/or "cell proliferation polypeptide marker", the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts.

Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Though $p16^{INK4a}$ and Ki-67 may be fully characterized antigens, the claims are not limited to an antibody that binds $p16^{INK4a}$ or Ki-67, but includes any antibody that binds to any one of a genus of "INK4a polypeptides" and any antibody that bind to any one of a genus of "cell proliferation polypeptide markers".

Neither the "INK4a polypeptide" nor the "cell proliferation polypeptide markers" is necessarily a well characterized antigen that has been described by the prior art.

Presumably the "INK4a polypeptide" may be any polypeptide that either shares the recited nomenclature, or which perhaps is encoded by the *INK4a* gene, including, for example, any allelic variant or mutant form thereof encoding a structural and/or functional variant of $p16^{INK4a}$ (e.g., an isoform or translation product of an alternatively spliced mRNA molecule). Then, too, according to claim 36, the "INK4a polypeptide" may be the product of an overlapping gene (i.e., *ARF*) occurring at the same locus as the *INK4a* gene, which encodes $p14^{ARF}$; so the claims might be construed as also encompassing any gene product (i.e., polypeptide) of an allelic variant or mutant form of *ARF* encoding a structural and/or functional variant of $p14^{ARF}$.

Notably, the transcripts encoding $p16^{INK4a}$ and $p14^{ARF}$ originate at two different upstream exons of the locus, which are designated 1α and 1β, but share an internal dual-coding exon 2; however, because $p16^{INK4a}$ and $p14^{ARF}$ are translated from alternative reading frames of exon 2, the two proteins share no sequence similarity.

Given these facts it is submitted that the description of either one of $p16^{INK4a}$ and $p14^{ARF}$, or both, cannot suffice to describe the "INK4a polypeptide" to which the claims are directed since it cannot be ascertained which features necessarily characterize the members of the genus of "INK4a polypeptides".

Then, although there are a large plurality of proteins that might serve as markers of "cell proliferation ", which have been described by the prior art, and some of which are listed with particularity in this application, the specific features that identify the "cell proliferation polypeptide marker" to which the claims are directed cannot be ascertained. It is therefore not evident what characterizes the one or more "cell proliferation polypeptide markers" to which the claims are directed.

Many so-called "cell proliferation polypeptide markers" are expressed exclusively by proliferating cells, though the claimed marker need not have such limited expression. Many of such proteins, which might be regarded as "cell proliferation polypeptide markers", are expressed during certain phases of the cell cycle, and not during others; but the claimed marker need not be expressed during any particular phase of the cell cycle. Many proteins might be expressed by certain proliferating types of cells, but not others; then again the claimed marker need not be expressed by any particular type of cell, which is proliferating.

Because it is not evident which features characterize the one or more "cell proliferation polypeptide markers" to which the claims are directed, the disclosure would not permit the skilled artisan to immediately envision, recognize or distinguish as least a substantial number of the genus of "cell proliferation polypeptide markers" to which the claims are directed.

Applicant is again reminded that “generalized language may not suffice if it does not convey the detailed identity of an invention.” *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

For these reasons, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

14. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a kit comprising

an antibody that specifically binds to $p16^{INK4a}$ and an antibody that binds to the Ki67/Ki-S5 antigen, **does not reasonably provide enablement for making and/or using** the claimed kits, which comprise one or more "probes" for the detection of the expression of at least one "INK4a polypeptide" and one or more "probes" for the detection of at least one "cell proliferation polypeptide marker". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims, as failing to satisfy the written description requirement, though the claims are not limited to a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that binds to the Ki67/Ki-S5 antigen, the specification provides an adequate of description of only that subject matter. It does not, for example, adequately describe any other "probe" that is suitable for use in detecting $p16^{INK4a}$ or Ki67, or any "probe", including an antibody that is suitable for detecting any of the plurality of structurally and/or functionally disparate members of the genus of "INK4a polypeptides" or the "cell proliferation polypeptide markers" to which the claims are directed.

What has not been adequately described cannot be made without undue and/or unreasonable experimentation; and what cannot be made cannot be used.

The specification, at best, provides an enabling disclosure for making and using a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that binds to the Ki67/Ki-S5 antigen; it would not, however, reasonably enable the skilled artisan to make and/or use the claimed kits, which comprise one or more "probes" for the detection of the expression of at least one "INK4a polypeptide" and one or more "probes" for the detection of at least one "cell proliferation polypeptide marker".

Though other materials and substances may be suitable for use in detecting $p16^{INK4a}$ or Ki67, it would not be without undue and/or unreasonable experimentation that such materials and substances might be identified since one cannot predict whether any given peptide or small organic molecule, for example, will specifically bind to $p16^{INK4a}$ or Ki67, so as to be useful as a probe for detecting $p16^{INK4a}$ or Ki67.

The amount of guidance, directed and exemplification set forth in the specification is not reasonably commensurate in scope with the breadth of the claims; and one could only identify suitable "probes" for use in detecting $p16^{INK4a}$

or Ki67 by empirically testing the ability of different materials and substances (e.g., peptides and small organic molecules) for such suitability.

Applicant is therefore reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a "probe" suitable for use in detecting $p16^{INK4a}$ or Ki67; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

> matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 35-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al. (*Am. J. Pathol.* 2000 May; **156** (5): 1573-1579).

Here the claims are directed to a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen.

Martin et al. describes a study in which antibodies that specifically bind to $p16^{INK4a}$ or Ki67 were used; see entire document (e.g., the abstract). Moreover, Martin et al. describes an experiment in which cells expressing $p16^{INK4a}$ and/or Ki67 were "double labeled" with antibodies that bind to $p16^{INK4a}$ or Ki67, so as to permit simultaneous detection of the antigens; see, e.g., page 1574, column 2.

Martin et al. teaches kits comprising reagents for the detection $p16^{INK4a}$ or Ki67 (see, e.g., page 1574, column 2), but does not expressly teach a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen.

Nonetheless, in light of the disclosure by Martin et al., and in view of teachings, suggestions, or other motivation found in the knowledge generally available to one of ordinary skill in the art at the time the invention was made, it would have been *prima facie* obvious to one of ordinary skill in the art at the time to have manufactured a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen, since, in particular, Martin et al. teaches an dual analysis of the levels of $p16^{INK4a}$ and Ki67in cells using detectably labeled antibodies that specifically bind to $p16^{INK4a}$ or Ki67. Given such disclosure, it follows logically that a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen could be used to detect $p16^{INK4a}$ and the Ki67/Ki-S5 antigen; so therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to do so since such kits had become widely used in such research, having established utility in such expression studies, for

example, and providing ease of use and convenience, as well as greater uniformity and control.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit a "positive control", namely a sample of $p16^{INK4a}$ polypeptide, which could be used in assays designed to access the presence of $p16^{INK4a}$ in biological samples. The use of such positive controls was routine and conventional at the time. The inclusion of such a positive control in the kit would greatly ease use of the kit to detect $p16^{INK4a}$ in biological samples because it would not have been necessary to develop a positive control, where one has already been provided.

Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit labeled antibodies that specifically bind to $p16^{INK4a}$ or the Ki67/Ki-S5 antigen since such antibodies could be used directed without the need of secondary antibodies and indirect labeling methods. The inclusion of such labeled antibodies in the kit would greatly ease use of the kit to detect $p16^{INK4a}$ and Ki67 in biological samples because it would not have been necessary to acquire and use secondary antibodies and indirect labeling reagents. There were at the time many different "labels" that might have been used, including, for example, fluorescent labels having different emission spectra, which would permit simultaneous measurements to be made where more than one fluorescently labeled antibody is used at the same time to stain cells expressing one or both antigens.

Conclusion

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Both Dai et al. (*Gastroenterol.* 2000 Oct; **119** (4): 929-942) and Emig et al. (*Br. J. Cancer.* 1998 Dec; **78** (12): 1661-1668) teaches an analysis of the levels of p16 and Ki67 in the same samples.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/

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slr
July 20, 2008